



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
CHEMICAL SAFETY AND  
POLLUTION PREVENTION

**MEMORANDUM:**

**From:** Kevin Sweeney, Senior Entomologist

*Jeffrey* 12/6/13

**Date:** December 6, 2013

**Subject:** PRODUCT PERFORMANCE DATA EVALUATION RECORD

**This review is for Tasks 137 and 139 to evaluate the speed of kill claim on cats: "Starts Killing in 30 minutes". Primary reviews are attached.**

**Task 137**

**DP barcodes:** 412772

**Decision no.:** 479788

**Submission no:** 936716

**Action code:** R340

**Product Name:** Hartz Reference #129

**EPA Reg. No or File Symbol:** 2596-164

**Formulation Type:** pet spot-on

**Ingredients statement from the label with PC codes included:** 9.7% fipronil (pc code: 129121)

**Application rate(s) of product:** 0.5 ml

**Use pattern:** spot-on for cats. Apply in one spot between the shoulder blades.

**OCSPP/OPPTS Guidelines:** OPPTS 810.3300.

**Task 139**

**DP barcodes:** 412943

**Decision no.:** 479891

**Submission no:** 936811

**Action code:** R340

**Product Name:** Hartz Reference #131

**EPA Reg. No or File Symbol:** 2596-166

**Formulation Type:** pet spot-on

**Ingredients statement from the label with PC codes included:** 9.8% fipronil (pc code: 129121) and 11.8% (S)-methoprene (pc code: 105402)

**Application rate(s) of product:** 0.5 ml

**Use pattern:** spot-on for cats applied in one spot between the shoulder blades.

**OCSPP/OPPTS Guidelines:** OPPTS 810.3300.



**I. Action Requested:** Review efficacy data in support of a label amendment to add new speed of kill claims to a cat spot-on. Registrant wants to claim that the product starts killing in 30 minutes.

**II. Background:** Registrant submitted two copies of one study and each copy was assigned a unique MRID. As a result, the same study was reviewed twice, once for each product.

### **III. Study Reviews:**

**These two MRIDs are the same.**

**MRID 49151101. Everett, W.R. Speed of Kill Efficacy of a Dermal Treatment Applied to Cats Against Cat Fleas (*Ctenocephalides felis*). March 26, 2013.**

**MRID 49153801. Everett, W.R. Speed of Kill Efficacy of a Dermal Treatment Applied to Cats against Cat Fleas (*Ctenocephalides felis*). March 26, 2013.**

**Purpose:** to determine the speed of kill of 9.7% fipronil in a solvent base. These data were not product specific because the adulticide component needed to be tested separately for the speed of kill determination.

**The primary review explains the details of the methodology used and the lists the results. Raw data were provided but were summarized by animal id on page 19 of the study.**

There was a treated (Group 1) and an untreated group (Group 2) with 8 cats each. Blocks were assigned and consisted of 2 cats each. Cats were treated with the test substance on Day 0. The test substance was applied to a spot between the shoulders. On Day +2 each cat was infested with 100 adult fleas applied to the lateral midline on both sides of the animal. The animal was restrained by hand while fleas were applied to enable the fleas to infest the cat. Comb counts were conducted at 15 minutes, 30 minutes, 1 hour, and 2 hours post-infestation. Data were pooled and analyzed using a test that was described as the equivalent as a one-way ANOVA.

A significant difference between the treated and control groups occurred at 2 hours post-infestation (on post-treatment day +2). The efficacy is the treatment group was a 37.5% reduction in fleas compared to the control group. This difference, though significant, was much lower than the 90% level EPA uses as the benchmark for efficacy success.

### **IV. ENTOMOLOGIST'S COMMENTS AND RECOMMENDATIONS:**

1. The claim "Starts killing fleas in 30 minutes is not acceptable" and should be removed. The data indicated a significant difference at two hours post-infestation on Day +2 after product treatment. However, the speed of kill efficacy was poor – at 37% - and does not substantiate the claim. This decision is consistent with related claims such as "Quick Knockdown" or "Quick



Kill” for other product types where 90% or greater knockdown or kill is described at a time interval. The time interval is usually identified as the  $LT_{90}$  value. The study should have been designed to measure time to 90% kill as the means of expressing speed of kill.

Also claims of this type should fully describe the speed of kill – “Starts killing x days after application” instead of minutes or hours – which accurately reflect the submitted data.



## TASK 2 DATA EVALUATION RECORD

**STUDY TYPE: Product Performance**

**MRID 491511-01. Everett, W.R. Speed of Kill Efficacy of a Dermal Treatment Applied to Cats Against Cat Fleas (*Ctenocephalides felis*). March 26, 2013.**

**810.3300: Treatments to Control Pests of Humans and Pets.**

**Product Name: Hartz® Reference # 129**

**EPA Reg. No. or File Symbol: 2596-164**

**Decision number: 479788**

**DP number: 412772**

Prepared for  
Registration Division (7505)  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
Washington, DC 20460

Prepared by  
Summitec Corporation  
Task Order No.: 2-137

Primary Reviewer:  
Robert H. Ross, M.S.

Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

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Signature: \_\_\_\_\_  
Date: \_\_\_\_\_

### Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

Summitec Corp. for the U.S. Environmental Protection Agency under Contract No. EP-W-11-014

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## DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

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|                                |   |
|--------------------------------|---|
| <b>STUDY TYPE:</b>             | 810.3300: Treatments to Control Pests of Humans and Pets.   |
| <b>MRID:</b>                   | 491511-01. Everett, W.R. Speed of Kill Efficacy of a Dermal Treatment Applied to Cats Against Cat Fleas ( <i>Ctenocephalides felis</i> ). March 26, 2013. |
| <b>DP BARCODE:</b>             | 412772  |
| <b>DECISION NO:</b>            | 479788  |
| <b>SUBMISSION NO:</b>          | 936716  |
| <b>SPONSOR:</b>                | W. Lance Hemsarth<br>The Hartz Mountain Corporation   |
| <b>TESTING FACILITY:</b>       | BerTek, Inc.<br>104 Wilson Bottoms Road<br>Greenbrier, AR 72058   |
| <b>STUDY DIRECTOR:</b>         | William R. Everett, Ph.D.<br>President/Laboratory Director<br>BerTek, Inc.  |
| <b>SUBMITTER:</b>              | Sean McNear<br>The Hartz Mountain Corporation   |
| <b>STUDY COMPLETED:</b>        | 26/03/2013  |
| <b>CONFIDENTIALITY CLAIMS:</b> | None  |



**GOOD LABORATORY  
PRACTICE:**

This study was conducted in accordance with the EPA Good Laboratory Practice Standards (40 CFR 160). The following exceptions are noted.

1. The commercial animal ration used in the study was not analyzed for specific contaminants because none were expected.
2. The drinking water used in the study was not analyzed for specific contaminants because none were expected. This was potable water obtained from the local public water supply. The water is routinely analyzed by the local water authority for suitability as drinking water.

**TEST MATERIAL:**

PRODUCT NAME: Hartz® Reference # 129  
EPA REGISTRATION NUMBER OR FILE SYMBOL:  
2596-164  
ACTIVE INGREDIENT NAME: Fipronil  
CHEMICAL NAME: Not given  
A.I. %: 9.70  
PC CODE: 129121  
CAS NO.: Not given  
FORMULATION TYPE: Topical Solution  
PRODUCT APPLICATION RATE(S) : One tube (0.5  
mL) once a month  
ACTIVE INGREDIENT APPLICATION RATE(S)g: Not  
given

**PROPOSED LABEL  
MARKETING CLAIMS:**

Rapidly eliminates fleas; starts killing within 2 hours

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**STUDY REVIEW**

**Purpose:** To determine speed of kill of Hartz® Reference # 129 for fleas on cats.

**MATERIALS AND METHODS**

**Test Location:** BerTek Laboratory, Greenbrier, AR

**Test Material(s):** Tubes containing 0.5 mL of 9.642% fipronil

**Test Species Name, Life Stage, Sex and Age:** Cat fleas (*Ctenocephalides felis*)



**Describe test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted:** Twenty-two cats were initially selected and 16 (8 for treated group and 8 for control group) with the highest pretreatment flea counts were selected for testing. A syringe (no needle) was used to apply 0.05 mL of the test product to each cat's back between the shoulder blades. 100 fleas were used for each infestation (4 per animal). Fleas were removed in between infestations. The activity schedule is below.

| Date        | Test Day | Activity   |
|-------------|----------|--|
| 28 Feb 2013 | Day -10  | <ul style="list-style-type: none"> <li>• Start acclimation.</li> <li>• Start daily health observations.</li> <li>• Bathe Cats</li> </ul>   |
| 04 Mar 2013 | Day -6   | <ul style="list-style-type: none"> <li>• Physical Exams</li> <li>• Pre-treatment flea infestation for qualification purposes.</li> </ul>   |
| 05 Mar 2013 | Day -5   | <ul style="list-style-type: none"> <li>• Pre-treatment flea count for qualification purposes</li> <li>• Weigh cats.</li> </ul>   |
| 08 Mar 2013 | Day -2   | <ul style="list-style-type: none"> <li>• Allocate cats to treatment groups.</li> </ul>   |
| 10 Mar 2013 | Day 0    | <ul style="list-style-type: none"> <li>• Treatment with test substance.</li> <li>• Post-dose observations (approx. 1h, 2h, 4h and 8h).</li> </ul>  |
| 12 Mar 2013 | Day 2    | <ul style="list-style-type: none"> <li>• Flea infestations for Speed of Kill evaluation (four)</li> <li>• Flea counts for Speed of Kill evaluation (15 min, 30 min, 1hr and 2 hr after respective infestations)</li> </ul> |

**List the treatments including untreated control:** 0.50 mL of 9.7% fipronil applied once per cat; untreated controls

**Number of replicates per treatment:** 16

**Number of individuals per replicate:** 400 fleas per cat

**Length of exposure to treatment (time in seconds, minutes or hours):** 2 days

**Were tested specimens transferred to clean containers?** NA

**Experimental conditions (state relative humidity, temperature, and photoperiod):** Laboratory conditions

**Data or endpoints collected/recorded:** Speed of kill at 15 and 30 minutes and at 1 and 2 hours



### Data analysis:

All analyses and calculations were performed by Sponsor assigned biostatistician using SAS Version 9.3. Statistical significance was declared at a two-sided p-value of 0.05.

Adult flea counts were transformed to the natural logarithm of (count + 1) to calculate geometric means. Percent efficacy for each treatment group on each day was calculated as

$$100 * (GMC - GMT) / GMC$$

where GMC = geometric mean of the control group and GMT = geometric mean of the treated group.

The transformed data were analyzed using t-tests for means with poolable variances or for means with unequal variances, as appropriate; variances were compared using the maximum-F test and Satterthwaite's Approximation was used to determine the degrees of freedom for the unequal-variance tests. The t-test is equivalent to one-way ANOVA when variances are poolable, and is more appropriate than one-way ANOVA when variances are found to be unequal. The treated group was compared to the control group.

### RESULTS

Table 1 shows that the speed of flea kill compared to controls.

*Table 1. Summary of geometric mean<sup>1</sup> flea counts (and percent efficacy) for cats treated with TS# 13801 at 0.50 mL, or remaining untreated*

| Time after infestation | Control | TS# 13801         | Efficacy | p-value             |
|------------------------|---------|-------------------|----------|---------------------|
| 15 minutes             | 78.3    | 85.8              | --       | >0.10 <sup>E</sup>  |
| 30 minutes             | 86.6    | 83.6              | 3.4%     | >0.10 <sup>U</sup>  |
| 1 hour                 | 88.5    | 76.5              | 13.7%    | 0.0502 <sup>E</sup> |
| 2 hours                | 82.1    | 51.4 <sup>B</sup> | 37.5%    | 0.0003 <sup>E</sup> |

<sup>B</sup> Significantly different from control (p<0.01)

<sup>1</sup> Based on transformation to natural logarithm of (count + 1)

<sup>E</sup> Results from t-test for means with poolable variances

<sup>U</sup> Results from t-test for means with unequal variances



### **Study Author's Conclusions**

Cats treated with TS# 13801 had significantly ( $p < 0.01$ ) lower flea counts than the controls at 2 hours after infestation. At 15 and 30 minutes after infestation, the flea counts of the two groups did not differ significantly ( $p > 0.10$ ). At 1 hour after infestation, the two groups were almost significantly different with a p-value of 0.0502.

### **Reviewer's Conclusions**

Within the first two hours, the speed of kill was not that impressive.

### **Reviewer's Recommendations**

Two days after a spot-on treatment with the subject product fleas begin to die. At two hours on day 2, the number of fleas on control and treatment animals is significantly different. However, the level of efficacy is low – 37%.

The label claim as proposed on the new label “starts killing within 2 hours” does not mention that this speed of kill begins to occur two days after the treatment. Second, the registrant is proposing that claim be supported by a level of efficacy that is less than 90%.